Changes in cardiovascular risk and clinical outcomes in a HIV/AIDS cohort study over a 1-year period at a specialized clinic in Mexico

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Introduction: The third report of the National Cholesterol Education Program guidelines recommends calculating the 10-year morbidity of atherosclerotic cardiovascular disease (ASCVD) using risk calculators when treating high blood cholesterol in adults. We analyzed the changes in cardiovascular risk (CVR) among Mexican patients with HIV.

Patients and methods: This observational, prospective cohort study compared the CVR after 1 year of antiretroviral treatment among 460 HIV patients from a Mexican clinic. Changes using the ASCVD risk estimator and changes in clinical outcomes were analyzed. The results were categorized as low or high CVR using a cutoff of 7.5%.

Results: The CVR initially had a median of 2.3% (interquartile range [IQR]: 1%–4.8%), which changed to 2.4% (IQR: 1.5%–5.5%) after 1 year (P=0.001). After CVR stratification, we found that 84.3% of the patients had a low CVR, and 18% in this subgroup had metabolic syndrome (MS). Moreover, 15.7% had high CVR, and 47% in this subgroup had MS. The 4.3% of patients had an increase in CVR from the low to high subgroup, and 2.6% had a decrease in CVR from the high to low subgroup. Out of all patients, 22.3% had MS.

Conclusion: More than 50% of the population had an increase in CVR after 1 year. Of these patients, 4.3% changed from the low to high CVR group. Although the guidelines proposed different time periods for performing CVR estimations, this study showed that such assessments offered valuable clinical data over a relatively short-term period.

Keywords: cardiovascular risk factors, HIV, metabolic syndrome

Introduction

Because of the success of easier, less toxic, more effective, highly active antiretroviral therapies (HAARTs), the mortality of people living with HIV (PLWH) and AIDS has declined.[1,2] The factors that contribute to increased cardiovascular risk (CVR) in PLWH are complex because of inflammatory pathway activation and comorbidities that are associated with risk behaviors and lifestyle habits.[3] It is well known that HAARTs can induce metabolic abnormalities and increase toxicity markers such as serum cholesterol, triglycerides, and hepatic enzymes.[4,5] Underlying HIV infection per se might also result in an increased risk of CVR.[6] Increases in lipid levels promote lipoatrophy development, lipo-accumulation, and insulin resistance with consequent hyperglycemia and hyperlipidemia.[6–8] Chronic inflammatory processes in PLWH resulting from an imbalance in immune/inflammatory responses can increase the levels of systemic pro-inflammatory markers and adiponectin.[9]

Previous studies suggested that cardiovascular disease (CVD) is approximately 1.5- to 2-fold higher in PLWH vs noninfected people.[10,11] However, the specific CVR

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factors that result from the metabolic effects of HIV infection and its therapies suggest that useful approaches exist to screen for CVD in PLWH.[10]

National and international guidelines propose that multivariate risk tools such as the Framingham equations should be incorporated into CVR assessment.[12–16] In Mexico, CVR evaluation is recommended each year,[12] whereas Spain recommends evaluation every 2 years.[13] Studies in the US have used the Framingham assessment guidelines to address CVR management.[13] CVR evaluation in Mexican patients has not been documented to date. Nevertheless, studies have reported an increase in cardiovascular events in the United States.[14] Evidence from prospective, observational, and surrogate end point studies suggests that HAARTs are associated with an increased risk of cardiovascular events and are related in part to dyslipidemia. The American College of Cardiology/American Heart Association (ACC/AHA) clinical guidelines[15] emphasize CVR assessment for two reasons: 1) to address modifiable risk factors for reducing CVR in patients and 2) to demonstrate CVD risk reduction benefits. Both of these factors help determine whether a patient is at high risk and identify how to address any CVR factors present.[14,16] CVD risk reduction must be one of the primary goals of medical care; for that reason, this study sought to analyze the changes in the CVR and clinical outcomes of PLWH attending a specialized clinic over a 1-year period.

Patients and methods
Design
An observational and prospective cohort study was conducted to compare CVR among PLWH and clinical outcomes after 1 year of HAART (which is defined as a combination of three or more antiretroviral drugs to inhibit the replication of HIV) at a specialized clinic. The study was approved by the National Ethics Committee on Health Research and the Biosecurity Committee, which both belong to the Mexican Institute of Social Security (IMSS; number: F-CNCI-2015–156). Therefore, the study was performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent for publication was obtained from all the authors and participants.

Study participants
The sample consisted of registered outpatients from the Retrovirus Clinic of the Regional General Hospital Number 1 of the IMSS in Morelos, Mexico. Patients aged ≥18 years with complete clinical records were eligible for study inclusion.

Data collection
All patients' clinical records in February 2015 were analyzed; a second data analysis was conducted in February 2016. Each patient had a monthly medical appointment at the Retrovirus Clinic, in which anthropometric and blood pressure (BP) measurements were taken by a nurse. The physician specialist obtained a complete medical interview, physical examination, and laboratory findings from each patient. The patients received their monthly medication based on Mexican guidelines.[12] Other services such as social care and psychology were provided.

Initially, the following information was manually collected: 1) HIV/AIDS diagnosis date; 2) history of CVD (myocardial infarction [MI], stroke, or an intervention for coronary artery disease), type 2 diabetes mellitus (T2DM), and hypertension diagnosis date; 3) cigarette smoking status; 4) HAART regimen; and 5) hypoglycemic, antihypertensive, and lipid-lowering medication use.

Study variables
The outcome variables evaluated in this study included CVR assessment, clinical measures (systolic and diastolic BP, waist circumference, weight, and height), laboratory values (fasting glucose [FG], total cholesterol [TC], and high-density lipoprotein cholesterol [HDL-C]), triglycerides, CD4+ cell count, and metabolic syndrome (MS) profile. CVR calculation was performed using the atherosclerotic CVD (ASCVD) risk estimator recommended by the ACC/AHA clinical guidelines[15] to quantify the estimated 10-year absolute ASCVD risk at and after a 1-year period. The ASCVD estimator is based on a parametric statistical model controlling for multiple CVD risk factors including age, gender, race, TC, HDL-C, systolic BP, hypertension treatment, T2DM status, and smoking history. A CVR value of 7.5% was considered as the cutoff point for this study, because this percentage is used by the ACC/AHA[15] as a reference point for establishing the intensity of lipid-lowering therapy. When the CVR is ≥7.5%, the use of moderate-to-high statin therapy should be considered; when the CVR is <7.5%, a low-to-moderate intensity statin can be considered. In this study, <7.5% values were considered as "low CVR", and the ≥7.5% values were considered as "high CVR".

The MS profile was defined as the presence of three or more of the following National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria:[17] 1) waist circumference >88 cm in women or >102 cm in men; 2) BP ≥130 mmHg systolic or ≥85 mmHg diastolic or use of antihypertensive medications; 3) triglycerides ≥150 mg/dL or

use of lipid-lowering medications; 4) serum FG ≥100 mg/dL, physician-diagnosed diabetes or use of diabetic medications; 5) HDL-C <50 mg/dL in women or <40 mg/dL in men. These criteria reference values were used to compare the initial and 1-year period data as defined by the NCEP-ATP III criteria.[17]

Statistical analyses

Categorical variables were expressed as frequencies and percentages. The Pearson's chi-squared and Fisher's exact tests were used to calculate 95% CI for categorical variables. Non-normal distributed continuous variables were expressed as medians and interquartile ranges (IQRs), and differences were determined using Wilcoxon signed-rank test with a 5% error. All statistical analyses were performed using Minitab version 17 for Windows (Statistical software, State College, PA, USA).

Results

The sample consisted of 460 patients: 79.3% were men and 20.7% were women. The median age of the sample was 43 years (IQR: 34–52 years); women (46 years) were older than men (42 years) on average ($P<0.001$). Ninety-one (19.7%) patients were current smokers, 71 (15.4%) patients received antihypertensive treatment, 35 (7.6%) patients received T2DM treatment, and 219 (47.5%) patients received lipid-lowering treatment. We found MS and CVD event rates of 22.3% and 2.6%, respectively. The HAARTs applied in the current sample had a median duration of 6 years (IQR: 3–14 years); nucleoside reverse transcriptase inhibitor (NRTI) plus protease inhibitor (PI) was the most common therapy (Table 1).

The overall median CVR at baseline was 2.3% (IQR: 1%–4.8%), with a range of 0.2%–50.1%; after 1 year, the median was 2.4% (IQR: 1.1%–5.5%), with a range of

Table 1 Description of the characteristics among PLWH stratified by CVR at baseline

Variables	PLWH (n=460), n (%)	Low CVR (n=388), n (%)	High CVR (n=72), n (%)	P-value
Treatment				0.396
NRTI + PI	256 (55.7)	215 (55.4)	41 (56.9)	
NRTI + NNRTI	185 (40.2)	159 (4.1)	26 (36.1)	
NRTI + II	2 (0.4)	1 (0.3)	1 (1.4)	
Others	17 (3.7)	13 (3.4)	4 (5.6)	
Treatment with ABC as backbone				0.193
NRTI/ABC + PI	14 (3.0)	6 (1.3)	9 (12.5)	
NRTI/ABC + NNRTI	8 (1.7)	6 (1.5)	2 (2.8)	
MS risk factors				<0.001
Without	52 (11.3)	50 (12.9)	2 (2.8)	
1 and 2	306 (66.5)	270 (69.6)	36 (50.0)	
3 and 4	97 (21.1)	66 (17.0)	31 (43.1)	
5	5 (1.1)	2 (0.5)	3 (4.2)	
Current cigarette smoking				<0.001
Yes	91 (19.8)	69 (17.8)	22 (30.6)	
No	369 (80.2)	319 (82.2)	50 (69.4)	
Antihypertensive treatment				<0.001
Yes	71 (15.4)	39 (10.1)	32 (44.4)	
No	389 (84.6)	349 (90.0)	40 (55.6)	
T2DM treatment				<0.001
Yes	35 (7.6)	14 (3.6)	21 (29.2)	
No	425 (92.4)	374 (96.4)	51 (70.8)	
Lipid-lowering treatment				<0.001
Yes	219 (47.6)	177 (45.6)	42 (58.3)	
No	241 (52.4)	211 (54.4)	30 (41.7)	
CVD events				0.680
Yes	12 (2.6)	6 (1.6)	6 (8.3)	
No	448 (97.4)	382 (98.5)	66 (91.7)	

Notes: *P*-values between the low and high CVR groups were calculated with Pearson's chi-squared test or Fisher's exact test. MS risk factors, according to the NCEP-ATP III criteria.
Abbreviations: ABC, abacavir; ATP, Adult Treatment Panel; CVD, cardiovascular disease; CVR, cardiovascular risk; II, integrase inhibitor; MS, metabolic syndrome; NCEP, National Cholesterol Education Program; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; PLWH, people living with HIV; T2DM, type 2 diabetes mellitus.

Table 2 Metabolic and clinical parameters during the study of CVR assessment in PLWH

Variables	Low CVR			High CVR		
	n	Median	IQR	n	Median	IQR
CD4+ T cell (cells/mm³)	388[a]	540.5	381.3–756.2	72[a]	522.5	380.8–867.8
	388[b]	553	389–719.3	72[b]	585.5	399–812.5
	P-value	0.422			0.745	
FG (mg/dL)	388[a]	91	85–98	72[a]	94.5	87.3–115
	388[b]	93	87.3–100	72[b]	98	91–117
	P-value	<0.001[c]			0.032[c]	
TC (mg/dL)	388[a]	167.5	144–195	72[a]	170	146.5–211.5
	388[b]	173	149–196	72[b]	168	134–189.5
	P-value	0.004[c]			0.061	
HDL-C (mg/dL)	80[a]	44.5	36.3–54.8	11[a]	28	33–60
Women	85[b]	43	36–51	11[b]	53	35–57
	P-value	0.168			0.214	
HDL-C (mg/dL)	302[a]	37	32–43.25	62[a]	35	31.8–43.3
Men	302[b]	38	31–44	62[b]	37.5	30–43
	P-value	0.426			0.871	
Triglycerides (mg/dL)	388[a]	181	135–265	72[a]	201.5	152.3–282.5
	388[b]	180	126–248	72[b]	173	131.5–256
	P-value	0.053			0.006[c]	
Systolic BP (mmHg)	388[a]	113	104–120	72[a]	125	128–137
	388[b]	120	110–120	72[b]	120	110–124
	P-value	0.001[c]			<0.001[c]	
Diastolic BP (mmHg)	388[a]	70	63–79.75	72[a]	75	70–80
	388[b]	74	69.25–80	72[b]	75	66.5–80
	P-value	<0.001[c]			0.122	

Notes: P-values were calculated by Wilcoxon signed-rank test. [a]Baseline. [b]After a 1-year period. [c]Statistical significance.
Abbreviations: BP, blood pressure; CVR, cardiovascular risk; FG, fasting glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; PLWH, people living with HIV; TC, total cholesterol.

0.2%–33.2% ($P=0.001$). At the beginning, the patients with low CVR comprised 84.3% of the sample, and the group with high CVR comprised 15.7%. Patients with low CVR had a higher proportion of one or two MS risk factors and a higher MS percentage (18%) compared with the high CVR patient group ($P<0.001$). Lipid-lowering treatment was found in similar proportions between the low and high CVR groups.

After 1 year, we found that the low CVR group showed a CVR increase from 2.3% to 2.7% ($P<0.001$), and the high CVR group showed a CVR decrease from 16% to 14.2% ($P<0.001$).

The analysis of the CVR changes over the 1-year period showed that 84.3% (388) of study patients were classified as low CVR at baseline. We found that 34.3% (133/388) of study patients showed a decrease in CVR ($P<0.001$), whereas 57.7% (224/388) of study patients showed an increase in CVR ($P<0.001$). Within the latter group, 8.9% (20/224) patients had an increase in CVR >7.5%.

We found that 15.7% (72) study patients showed high CVR. Of these patients, 62.5% (45/72 patients) showed a decrease in CVR, and 24.4% (11/45) of patients switched to a low CVR value (Figure 1).

We found an increase in FG levels in the low and high CVR groups ($P<0.05$). The median triglyceride values in the high CVR group decreased ($P<0.05$) after a 1-year period (Table 2).

We performed a subgroup analysis with regard to extreme changes. Twenty patients had an increase in their CVR above the 7.5% value, and eleven had a decrease in their CVR below the 7.5% cutoff. In the low CVR subgroup, TC and BP increased ($P<0.05$). The high CVR group showed a decrease in TC, triglyceride levels, and BP ($P<0.05$; Table 3).

Discussion

Although some studies have suggested an association between MS and the risk of CVD and diabetes in PLWH, the role of MS as an independent predictor of CVD risk is unclear.[20] According to the NCEP-ATP III criteria, the frequency of MS in this cohort presents an intermediate tendency compared with other studies.[18–20]

Although the high CVR group reported large numbers of antihypertensive, hypoglycemic, and lipid-lowering prescriptions, the prevalence of MS was high most likely because of the extended time of HAART use and time of
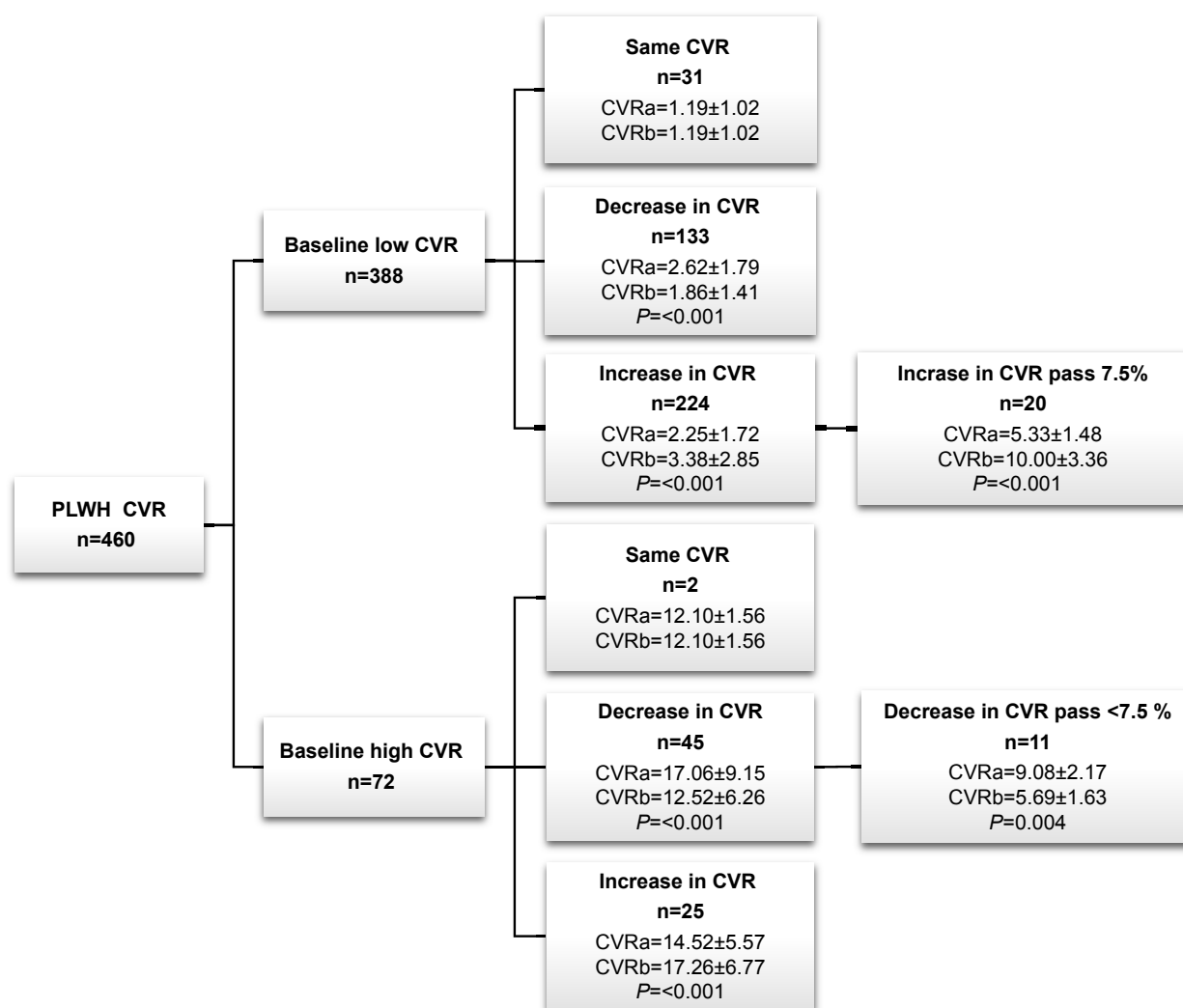
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                                    ┌─────────────────────────┐
                                    │      Same CVR           │
                                    │       n=31              │
                                    │  CVRa=1.19±1.02         │
                                    │  CVRb=1.19±1.02         │
                                    └─────────────────────────┘

                                    ┌─────────────────────────┐
                                    │   Decrease in CVR       │
                                    │       n=133             │
              ┌──────────────────┐  │  CVRa=2.62±1.79         │
              │ Baseline low CVR │  │  CVRb=1.86±1.41         │
              │      n=388       │  │  P=<0.001               │
              └──────────────────┘  └─────────────────────────┘

                                    ┌─────────────────────────┐     ┌─────────────────────────┐
                                    │   Increase in CVR       │     │  Incrase in CVR pass 7.5%│
                                    │       n=224             │     │       n=20              │
                                    │  CVRa=2.25±1.72         │─────│  CVRa=5.33±1.48         │
                                    │  CVRb=3.38±2.85         │     │  CVRb=10.00±3.36        │
                                    │  P=<0.001               │     │  P=<0.001               │
┌──────────────┐                    └─────────────────────────┘     └─────────────────────────┘
│  PLWH  CVR   │
│    n=460     │                     ┌─────────────────────────┐
└──────────────┘                     │      Same CVR           │
                                     │       n=2               │
                                     │  CVRa=12.10±1.56        │
                                     │  CVRb=12.10±1.56        │
                                     └─────────────────────────┘

                                     ┌─────────────────────────┐     ┌──────────────────────────┐
                                     │   Decrease in CVR       │     │  Decrease in CVR pass <7.5 %│
              ┌──────────────────┐   │       n=45              │     │       n=11               │
              │ Baseline high CVR│   │  CVRa=17.06±9.15        │─────│  CVRa=9.08±2.17          │
              │      n=72        │   │  CVRb=12.52±6.26        │     │  CVRb=5.69±1.63          │
              └──────────────────┘   │  P=<0.001               │     │  P=0.004                 │
                                     └─────────────────────────┘     └──────────────────────────┘

                                     ┌─────────────────────────┐
                                     │   Increase in CVR       │
                                     │       n=25              │
                                     │  CVRa=14.52±5.57        │
                                     │  CVRb=17.26±6.77        │
                                     │  P=<0.001               │
                                     └─────────────────────────┘
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Figure I Distribution of CVR changes in the study population; CVR according to the ASCVD risk estimator.
Notes: a, at baseline; b, after a 1-year period; P, calculated with Student's t-test.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVR, cardiovascular risk; PLWH, people living with HIV.

HIV diagnosis.[20–22] The presence of MS can increase CVD and diabetes risks.[19,20]

After CVR stratification, the analysis showed a significant CVR increase in 57.7% of the patients in the low CVR group after a 1-year period.

In the high CVR group, we found that PI plus NRTI was the most frequently used HAART, which was consistent with the Data Collection of Adverse Events due to Anti-HIV Drugs (DAD) study[6] and other studies,[23–25] in which the use of PI, a non-NRTI (NNRTI), or both, increased the CVD prevalence. Furthermore, when a PI, an NNRTI, or both are prescribed, the risk of MI increased up to 26% each year.[26] Our study found an MI prevalence of 2.6%, which was potentially related to the previous use of PI and NNRTI.

The results of a T2DM diagnosis in our study were not surprising because of the elevated prevalence of this disease in Mexico; however, it differed from those in the DAD study.[27] The FG increased in the low CVR group; however, this value remained at a controlled level according to the NCEP-ATP III recommendations. This increase might be the result of inducing decrements in insulin sensitivity resulting from PI treatment use.[8,27]

The low CVR group in our study showed a significant increase in TC, and this factor was one of those that significantly changed among the patients who showed extreme changes in CVR. The NRTI + PI regimens were mostly used for the low and high CVR groups as in previous studies,[6,8] in which patients undergoing this regimen showed increases in TC levels compared with naive patients. HAARTs might contribute to CVD associated with an increased risk of atherosclerosis.[26,28] A triglyceride reduction was found in the low and high CVR groups, but it was not enough to achieve the NCEP-ATP III goals, in which the reduction was apparently due to the wide use of statin therapy. Moreover, its use

Table 3 Metabolic and clinical changes among PLWH with extreme CVR changes

Variables	Low CVR (high increase in CVR[a])			High CVR (high decrease in CVR[b])		
	n=20	Median	IQR	n=11	Median	IQR
CD4+ T cell (cells/mm³)	20[c]	506.5	285.3–785.3	11[c]	531	432–928
	20[d]	577	277.8–893.3	11[d]	576	453–814
	P-value	0.263			0.534	
FG (mg/dL)	20[c]	98	90.5–109.3	11[c]	92	86–112
	20[d]	100	84–111.5	11[d]	99	96–124
	P-value	0.076			0.286	
TC (mg/dL)	20[c]	164	136.5–199	11[c]	188	178–226
	20[d]	187	160–211	11[d]	163	134–188
	P-value	0.026[e]			0.006[e]	
HDL-C (mg/dL)	20[c]	33	30–39.5	11[c]	35	32–40
	20[d]	35	28.8–40.3	11[d]	35	29–42
	P-value	0.747			0.609	
Triglycerides (mg/dL)	20[c]	219	167.3–337.3	11[c]	298	157–403
	20[d]	223	175–320.8	11[d]	176	146–259
	P-value	0.658			0.026[e]	
Systolic BP (mmHg)	20[c]	116.4	107.8–129.3	11[c]	126	121–137
	20[d]	124.5	115.5	11[d]	120	110–124
	P-value	0.015[e]			0.003[e]	
Diastolic BP (mmHg)	20[c]	74	61.25–80	11[c]	80	78–90
	20[d]	80	70.5–90	11[d]	80	70–80
	P-value	0.034[e]			0.046[e]	

Notes: P-values were calculated by Wilcoxon signed-rank test. [a]<7.5% change to ≥7.5% from low CVR to high CVR at follow-up. [b]≥7.5% change to <7.5% from high CVR to low CVR at follow-up. [c]Baseline. [d]After 1-year period. [e]Statistically significant.
Abbreviations: BP, blood pressure; CVR, cardiovascular risk; FG, fasting glucose; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; PLWH, people living with HIV; TC, total cholesterol.

in this population might explain the CVR changes over a 1-year period.

The CD4+ cell count of our sample increased after a 1-year period. Although this result was not significant, it revealed a desirable immunological trend in these patients. Previous reports have shown that CVR factors and a low CD4+ cell count are independently associated with the risk of CVD events.[29] Better approaches for analyzing the immunological contributions from CD4+ cells are required.

Our results provide valuable information concerning the identification of CVR factors in a population of Mexican PLWH, suggesting that the assessment of such risk factors leads to CVR improvements and, consequently, CVD prevention. Although the NCEP-ATP III results strongly suggest measuring lipid profiles, they do not provide specific recommendations regarding how often CVR should be addressed in PLWH. However, our findings suggest that a CVR assessment each year is reliable enough to detect the variations that can lead to CVD.

Study limitations

The design used for this study was limited to only observing and analyzing CVR changes; it did not analyze the therapeutic interventions performed during the year. Clinical information was missing from patient's records, including family histories of dyslipidemia and T2DM in addition to low-density lipoprotein cholesterol (LDL-C) measurements. Information about patients' alcohol use was also missing. It was not possible to completely analyze the quality of the lipid-lowering treatments in the study sample because of the missing data. Our study did not have a control group.

Conclusion

More than 50% of PLWH in this sample had an increase in CVR after 1 year. Of these patients, 4.3% were those who changed from the low to high CVR group. The CVR estimator showed usefulness as a potential routine CVR assessment tool in the studied Mexican population. The opportune assessment of the risk factors that determine increases in CVD among PLWH in addition to the use of the CVR estimator should be employed routinely by medical practitioners working in the HIV/AIDS field. Opportune detection and interventions that address modifiable risk factors should be implemented and evaluated to improve the patients' quality of life. Although the guidelines proposed different time periods for performing CVR estimations, this study showed that such assessments offered valuable clinical data over a relatively short-term period.

Availability of data and materials

Acknowledgments

Author contributions

Study design, data collection, data analysis, and manuscript writing: AC-P. Study design, data analysis, and manuscript writing: MAS-A. Study design and manuscript writing: SG-J. Study design and manuscript writing: EP-M. Study design and manuscript writing: GB-F. Manuscript writing: MC-M. Data analysis and manuscript writing: LA-J. Study design, data collection, data analysis, and manuscript writing: CDT-J. All the authors read and approved the final manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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